

OXITEC MOSQUITOES: EUP AND REGISTRATION APPLICATIONS

STATUS AND NEXT STEPS

Status and Background

➤ Experimental Use Permit (EUP)

Status: Oxitec's response to 10-day deficiency letter received (April 09, 2018); response remains deficient.

Action: BPPD is drafting a rejection letter while finalizing the human health and ecological effects screening memoranda.

Deadline for Action: July 25, 2018 (final PRIA date); EPA expects to make a final screen determination soon. Considering the 200,000+ comments already received, EPA is unlikely to reach a decision by July 25, 2018 if the application is not rejected.

2nd Public comments: Public participation closes June 07.

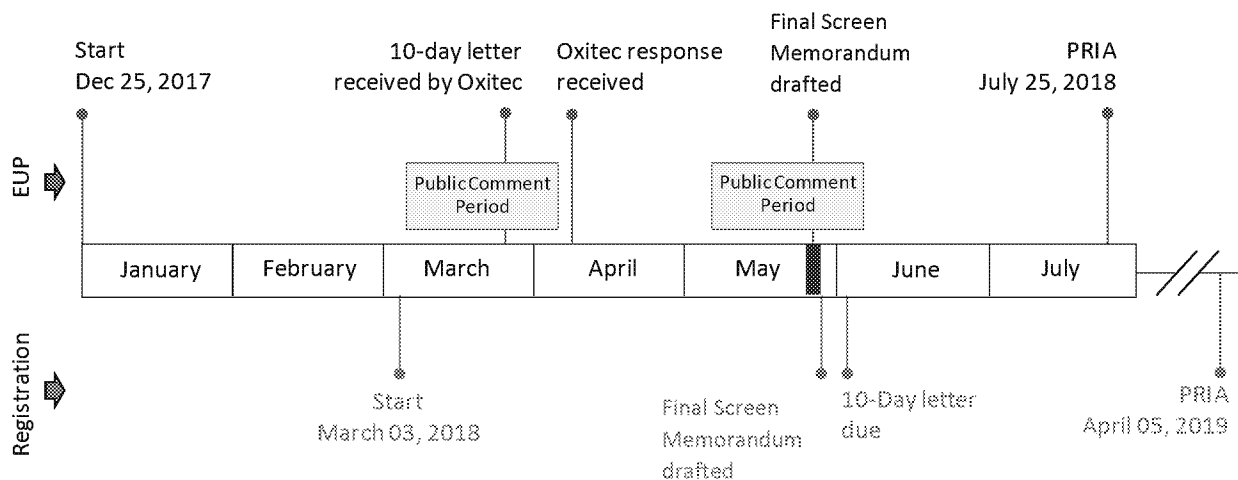
➤ Registration

Status: 90-day screen reviews drafted: Same deficiencies identified as for EUP plus foreign efficacy data. Caaman Island data and raw data for all foreign efficacy data needed. Most studies were identical to studies submitted in support of EUP, including studies submitted in response to the EUP 10-day deficiency letter.

Action: BPPD is drafting a 10-day deficiency letter while finalizing the human health and ecological effects screening memoranda.

Deadline for Action: June 04, 2018 (90-day screen deadline); deadline for sending the 10-day deficiency letter.

Notice of Receipt: Drafted, not published.



Two Key Deficiencies Identified for both EUP and Registration Applications

1. Uncertainties on the potential for DsRed2 (designated inert) to be allergenic.
2. Amounts of tTAV and DsRed2 proteins in OX513A mosquitoes and saliva not demonstrated.

This information is crucial to conduct the scientific risk assessments because exposure to the pesticide components and associated risk cannot be accurately estimated without this information. Based on Oxitec's data, some OX513A adult females carrying the tTAV and DsRed2 traits are expected to survive in the environment and possibly expose humans to these proteins through biting. Other non-target organisms would also be exposed to these proteins at undetermined levels.

Background on Key Deficiencies

- Once released into the environment, OX513A will mate with wild-type *Aedes aegypti* females. Due to incomplete penetrance of the pesticidal trait, some of the hemizygous offspring are expected to develop into adults even in the absence of tetracyclines. Studies conducted under controlled conditions indicate that about 20% of the surviving adult females are able to take two blood meals and lay two clutches of eggs. Although biotic and abiotic factors in the environment are generally expected to reduce survival of these females, the presented information is not sufficient to conclude that exposure to biting OX513A *Aedes aegypti* females, carrying the tTAV and DsRed2 traits, is negligible. Understanding the potential for tTAV and DsRed2 to be toxic or cause an allergic reaction is therefore necessary to define the risks of OX513A to human health and other non-target organisms.
- Positive queries in the AllergenOnline database raised the possibility that DsRed2 is an allergen (U.S. EPA, 2018). CODEX guidelines provide a threshold for the sequence identity to known or suspected allergens that are retrieved in this manner to aid in identifying novel putative allergens; DsRed2 exceeded that threshold. The protein has significant identity to a novel putative allergen, the GFP-like protein named Akane (Kato *et al.*, 2017). Prompted by an inquiry from Oxitec prior to issuance of the 10-Day Deficiency Letter, the panel of subject-matter experts at AllergenOnline removed Akane from their entry and issued a statement that outlined the panel's rationale to reverse its decision. The statement did not reveal any new information beyond what is presented in the Kato *et al.*, 2017 article, and which had initially served as the basis for the protein's adoption into the AllergenOnline database. Oxitec provided this letter to support the rationale that DsRed2 is not allergenic. In this context it is worth noting that COMPARE, a separate allergen database that is also lead by a group of subject-matter experts, has also adopted Akane as a putative allergen (as of signature date). Due to the significant identity of DsRed2 to Akane (CODEX) and the data presented by Kato *et al.*, 2017, the Agency cannot exclude that DsRed2 is a putative allergen.
- The primary route of exposure for humans to the tTAV and DsRed2 proteins is expected to be through biting OX513A homo- and hemizygous females. Therefore, it is important to assess if the proteins are present in mosquito saliva. In their response to the 10-Day deficiency letter, the applicant describes that the tTAV construct is active in mosquito salivary glands (NIH report), which raises the possibility that both proteins could also be present in the saliva. The presented Western blot analyses were deemed insufficient to determine the absence of either protein in the saliva, in part due to the lack of adequate positive controls. Without these data, the remaining body of evidence is not sufficient to exclude the presence of tTAV and DsRed2 in the saliva.